

Antimicrobial drug development – the past, the present, and the future

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ABSTRACT

Antimicrobial resistance has been an issue since the introduction into clinical use of the first agents in the 1940s. Although the discovery and development of new classes of antimicrobials through the 1960s presented an array of treatment options, these options for some serious and life-threatening infectious diseases may now be more limited. This paper examines the history of antimicrobial development, showing how the challenges in discovering new classes of drugs have been with us for the last 40 years. The present state of antimicrobial discovery and development is shaped by these challenges as well as by the economic realities of the pharmaceutical industry. This paper also discusses some of the regulatory considerations in antimicrobial drug development, and presents some potential solutions to the challenges inherent in antimicrobial drug development, including steps taken by the US Food and Drug Administration to streamline the drug review process for antimicrobial agents while maintaining the standards necessary to protect and promote the health of the public.

Keywords Antimicrobial resistance, drug development, drug design, clinical trials

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INTRODUCTION

The introduction of antimicrobial agents into general clinical use represents one of the landmark medical advances of modern medicine. In the last half of the 20th century, a number of new antimicrobials came into clinical use, presenting clinicians with an array of choices when treating many types of infectious diseases. However, the issue of antimicrobial resistance that has been a concern ever since the beginning of the antimicrobial era, has taken on more importance recently. Clinicians are witnessing increasing rates of *in vitro* resistance among previously susceptible organisms and the emergence of intrinsically resistant organisms as pathogens in immunocompromised hosts. The spread of resistance has in turn limited the treatment options for some serious and life-threatening diseases. To curtail the development and spread of antimicrobial resistance will require both the preservation of current antimicrobials through their appropri-

ate use, as well as the discovery and development of new agents. While there is a need for new agents, some large pharmaceutical companies have decided to exit the area of antimicrobial development, especially antibacterial drug development [1]. This paper will examine the history of antimicrobial drug development, how it has influenced the present situation, where we stand today, and address some of the potential solutions for spurring future antimicrobial development, including the response from regulatory agencies such as the US Food and Drug Administration (FDA).

THE PAST

The earliest uses of antimicrobials constituted a dramatic impact in altering mortality in serious and life-threatening bacterial diseases compared with the absence of therapy in the pre-antibiotic era. The use of subcutaneous sulfanilamide lowered the mortality rate of acute meningococcal meningitis from 70–90% in the pre-antibiotic era to approximately 10% [2]. It did not require large studies or many patients to confirm the benefits of antimicrobials in these serious illnesses. Based upon these impressive results in the treatment of severe and life-threatening diseases, clinicians

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expanded the use of antimicrobials to less severe illnesses. This extrapolation was based upon the premise that antimicrobials affect the growth of micro-organisms and therefore should be beneficial in diseases where bacteria are implicated as the causative pathogens. This premise, however, did not take into account the self-resolving nature of many of these illnesses. Data from placebo-controlled trials to determine the magnitude of the clinical treatment effect of antimicrobials in many of these illnesses was, and still remains, lacking. As will be shown, this has important implications for the future study of antimicrobials in some of these diseases that are largely self-resolving.

The past uses of antimicrobials also demonstrated issues associated with the safety of these drugs. In fact, safety issues associated with antimicrobials have changed the face of public health. The deaths associated with use of Elixir of Sulfanilamide resulted in the passage of the Food, Drug and Cosmetic (FD&C) Act in 1938 [3]. The adverse effects associated with administration of thalidomide, a drug used to treat manifestations of leprosy, resulted in an amendment to the FD&C Act in 1962 which required drug sponsors to demonstrate the efficacy of a drug product in the disease under study. Prior to that time, a drug sponsor had to show only that a drug was safe in order to receive an approval for marketing. This amendment followed from the recognition that the risk of adverse events associated with drug usage should be balanced by the benefits achieved by use of the drug.

In the 30 years following the introduction of sulfonamides and penicillin, scientists discovered and developed a wide range of antimicrobials to treat bacterial diseases, presenting clinicians with a number of treatment options for most infectious diseases. The method of discovery of new agents was largely based on the methods of German and Swiss scientists from the late 19th century for evaluating naturally occurring compounds. Many new antimicrobials were discovered surreptitiously and by observation, such as the discovery of the original cephalosporin C-producing organism in sewer water [4]. Many other antimicrobials were developed by chemical modification of existing agents.

The discovery of new classes of antibacterial drugs, defined here as drugs with a completely novel mechanism of action, slowed in the late

Table 1. History of antibacterial drug introductions and approval

Year introduced	Class of drug
1935	Sulfonamides
Food Drug and Cosmetics Act 1938 →	
1941	β-lactams (Penicillin)
1944	Aminoglycosides
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/Lincosamides/Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitromidiazoles
1962	Quinolones
Kefauver-Harris Amendments 1962 →	
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

1960s. The last novel class of antibacterial prior to the year 2000 was described in 1968 (Table 1). The majority of antimicrobials introduced since that time have been chemical modifications of previously discovered classes of drugs. This is testament to the challenges inherent in the discovery of new agents. It is also important to note that the majority of antibacterials were introduced prior to the 1962 efficacy requirement of the FD&C Act.

In spite of a lack of new classes of agents, drug developers continued to introduce new agents within existing classes. Some of these agents had efficacy against diseases caused by pathogens that were resistant to previous 'generations' of the same class. In addition, some of the drugs demonstrated improved efficacy in certain diseases compared with previous drugs. For instance, third generation cephalosporins are effective in diseases caused by Gram-negative organisms and in diseases, such as acute bacterial meningitis, where first-generation cephalosporins are less effective. Other agents had similar efficacy but manifested a different safety profile or a more convenient dosing schedule. Other agents introduced during this time represented minor advances over previous agents within the class but did present clinicians with an expanded range of treatment options.

The absence of a variety of new drug classes since the 1960s is evident when one examines the history of the FDA approval of antibacterial agents (Fig. 1). From 1980 to 1989, the FDA

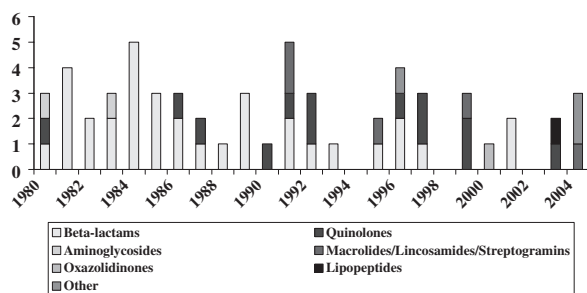


Fig. 1. Drug approvals by class: systemic antibacterials.

approved 29 new antibacterial drugs. Of these 29 agents, 24 were β -lactams, almost two-thirds of which were cephalosporins. From 1990 through 1999, the FDA approved 22 new antibacterial drugs with nine of these belonging to the quinolone class and eight belonging to the β -lactam classes.

With the approval of an increasing number of agents within classes and the lack of new drug classes, it is perhaps not surprising that development of antibacterial agents would reach a saturation point. In the 1960s, the FDA approved 2.9 new antibacterial drugs per year, which decreased to 2.2 drugs per year in the 1990s and 1.6 drugs per year so far since the year 2000. However, this decline is not unique to antibacterial drugs and reflects an overall decrease in the number of all new drugs submitted to the FDA over this time (Fig. 2) despite an increase in biomedical research spending (Fig. 3) [5]. This reflects the inherent

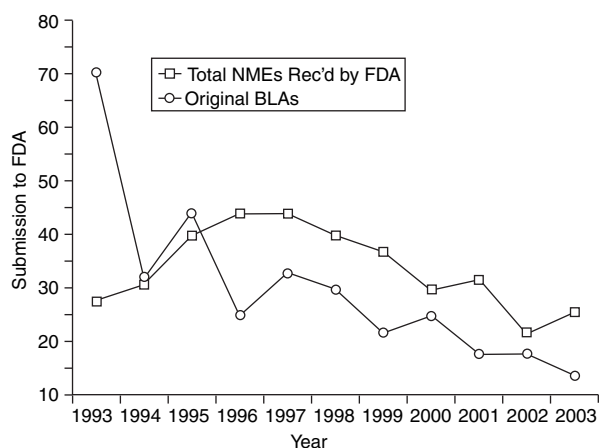


Fig. 2. Ten year trend in drug and biological new molecular entity (NME) submissions to FDA (from Reference 5).

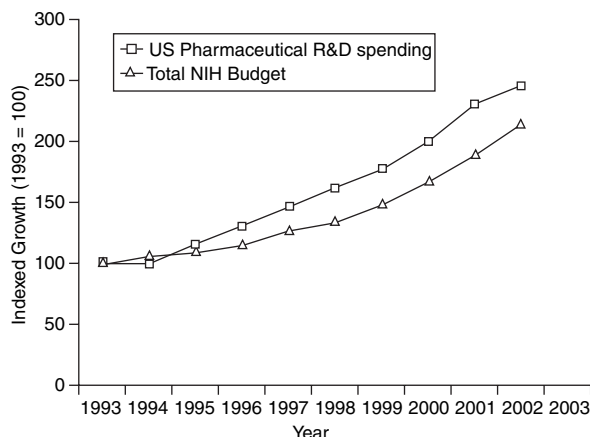


Fig. 3. Ten-year trend in biomedical research spending (from Ref. 5).

challenges in discovering and developing new drugs in any therapeutic class.

THE PRESENT

Today, antimicrobials are the third most profitable class of drugs for pharmaceutical companies, surpassed only by central nervous system and cardiovascular drugs. The market for antimicrobials is between \$26 bn [6] and \$45 bn per year. However, introducing an individual new antimicrobial, especially an antibacterial agent, to the marketplace may not be as profitable as other therapeutic classes of drugs. The best selling antibacterial made \$2.01 bn in 2003 but a lipid lowering agent sold by the same company made \$9.23 bn in that same year [7]. A recent study showed that the top five disease states, including heart disease, pulmonary conditions, mental disorders, cancer and hypertension, accounted for 31% of the increase in health care expenditures between 1987 and 2000 [8]. It follows that drugs to treat those conditions may be more profitable than those used to treat infectious diseases, which were number 13 on the list, accounting for 1.35% of the change in health care costs over that time.

There are several reasons why antibacterials may be at a competitive disadvantage relative to other drugs. There is a high level of competition with drugs already on the market. As shown above, there are a number of agents within various classes still available. While resistance is an emerging problem in a relative sense, the

majority of infectious diseases in terms of absolute numbers in the USA are still caused by susceptible pathogens. The impact of *in vitro* resistance may be greatest in serious and life-threatening diseases which, fortunately, are relatively less common compared with less serious illnesses in a developed country like the USA. This is evidenced by the fact that the majority of antimicrobials are prescribed on an outpatient basis. For instance, there are an estimated 4 million cases of community-acquired pneumonia yearly in the USA, but 3 million of those are treated as outpatients [9]. Also, clinicians may not perceive antimicrobial resistance as a problem, thereby decreasing the willingness of a drug sponsor to develop a drug for which there is not a perceived need. A recent study by the Centers for Disease Control (CDC) showed that the majority of clinicians consider antimicrobial resistance to be a national problem, but not one that they feel they encounter in their institutions or their own practices [10]. In addition, clinicians see the appropriate public health need to preserve older antimicrobial agents through judicious use, that is, not prescribing antibacterials to patients who do not have a bacterial infection. These patients cannot benefit from therapy but still may experience adverse effects in addition to harbouring and spreading resistant organisms. Experts often also recommend reserving new agents for patients who may have disease caused by resistant pathogens, limiting the potential use of a new drug. Finally, many antimicrobials are prescribed for treatment durations ranging from a single dose to 10 days of treatment. This short-term use limits the potential profitability of antibacterial drugs compared with other classes of drugs.

One can compare the development of antivirals with the development of antibacterials to see

these factors at work (Fig. 4). There are far fewer antiviral drugs already available than antibacterials, so there is less competition. Many antiviral drugs are for chronic illnesses like AIDS, and are prescribed long-term for the life of the patient. There is less of an issue of inappropriate prescribing, at least with some antivirals, such as anti-HIV drugs, since diagnostic tests can accurately select patients who require treatment, and the need for immediate treatment is less in a chronic illness than in a bacterial disease that may be rapidly fatal. Consequently, there has been an increase over time in the number of FDA approved antiviral drugs since 1980, with 0.4 drugs approved per year in the 1980s, 1.9 drugs per year in the 1990s and 1.2 drugs per year so far in this decade.

In addition, changes within the pharmaceutical industry itself may be contributing to the decrease in new antimicrobials [11]. In the last several years, a number of the larger pharmaceutical firms have merged to form even larger entities. According to members of the industry, larger firms require larger profits to sustain themselves, and may be less willing to develop drugs that are not 'blockbusters'. As discussed above, the diseases for which there appears to be the greatest need are also relatively less common, and drugs to treat these diseases would not usually be billion-dollar sellers. In addition, while some claim that only the resources of large companies can bring a product to market, other members of the pharmaceutical industry cite the 'diseconomies of scale' associated with bringing forward new ideas within a larger management structure of a bigger company [11].

Some authors have cited 'increased regulatory hurdles' for antimicrobials as one of the reasons companies have chosen to exit this field [12]. However, there are no increased regulatory hurdles for antimicrobials, or specifically antibacterials, compared with other therapeutic classes. Some have noted that sponsors of antibacterial drugs must perform several studies if the drug is to be approved for the treatment or prevention of a variety of infectious diseases. This is true of all therapeutic classes. An oncological drug is not approved for the treatment of 'cancer', but for specific forms of cancer, such as lung and breast cancer. Some antimicrobials, such as those that treat AIDS, treat one disease syndrome caused by one pathogen, but these are not

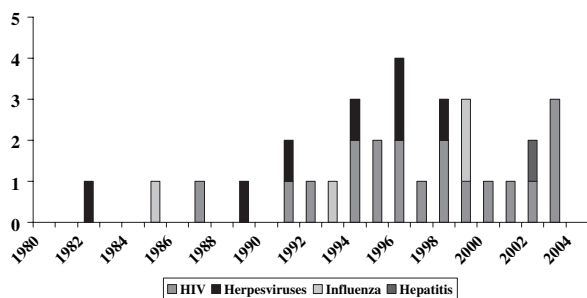


Fig. 4. Drug approvals by class: systemic antivirals.

'pathogen-specific' indications. When a virus can cause a variety of diseases, such as cytomegalovirus, the drug is approved for treatment of that specific disease, such as retinitis. It is clear that some drugs that may be effective in treating a disease at one body site may not be effective in treating diseases at another body site; therefore the need for separate studies is scientifically logical. A drug that may be effective in treating a urinary tract infection or pneumonia may not necessarily be effective in treating acute bacterial meningitis.

Other authors have also noted the difficulties in showing similarity of a new antimicrobial to a highly effective drug that is already on the market [13]. This challenge is not a 'regulatory hurdle' but a matter of good science and appropriate clinical trial design and interpretation [14]. The sample size required to show similar efficacy of a new drug to an already approved agent is usually larger than that required to demonstrate superiority of the new drug to other therapies. Authors have debated the issue of how much worse a new agent may be compared with the control drug and still claim 'similar' efficacy to the control. What is clear is that this 'noninferiority margin' cannot be greater than the benefit of the control drug relative to placebo or to no treatment. For instance, it is not logical to design a trial to show that the new drug can be as much as 10% less effective than the control drug when placebo-controlled trials show that the control drug may be superior to placebo by as little as 4%. This means that the new drug may not be any more effective than placebo.

Selecting the appropriate margin for noninferiority trials is more difficult when the margin of benefit of antimicrobials compared with placebo is not known. This is less of an issue in serious and life-threatening diseases like acute bacterial meningitis where the magnitude of the treatment benefits of antimicrobials is clear and very large. On the other hand, the magnitude of the treatment benefits of antimicrobials in some largely self-resolving illnesses like acute bacterial sinusitis is not clear and may be small. The sample size of clinical trials in infectious diseases is not larger than in other therapeutic areas. In fact, clinical trials in cardiovascular diseases can reach several thousand for a single trial, larger than the entire database of several studies contained in a New Drug Application (NDA) for an antimicrobial agent.

As stated above, the decrease in approvals of new antimicrobials reflects an overall trend in decreasing drug approvals in all therapeutic classes and a decrease in NDAs to the FDA [5]. Part of the high cost of bringing a new drug to market, quoted as \$800 m dollars, includes the cost of drugs that fail to make it through the development phase due to lack of efficacy or safety. It seems logical that the cost of drug development could be decreased by more accurate selection of drugs that are likely to achieve the goals of demonstrating safety and efficacy, and discontinuing early in development of drugs that will not prove to be safe and efficacious.

Despite the challenges in developing new antimicrobials, there are certain advantages for drug sponsors in developing antimicrobial agents. Antimicrobials have had the first or second shortest mean and median clinical development time compared with other therapeutic classes since 1982 [15]. Given the availability of preclinical *in vitro* testing and animal models as a first step in selecting appropriate compounds for further human clinical trials, antimicrobials have the highest approval success rates of any therapeutic class since 1964 [16].

THE FUTURE

A recent analysis showed that there are five new antibacterial drugs in development by large pharmaceutical companies [17]. This analysis does not evaluate drugs under development by biotechnology firms. At the present time, it is the experience at the FDA that more biotechnology firms are becoming involved in drug development of antimicrobials. This would seem to be the nature of capitalism; as one group decides to exit a given area, another group perceives an opportunity. At recent FDA meetings, members of biotechnology firms emphasised that the smaller markets of serious and life-threatening diseases are more attractive to smaller firms who can survive with smaller profits [1,18]. Some have questioned whether these firms will have the necessary resources to perform clinical trials to develop new drugs. However, venture capital firms have been quoted as stating that the need for large companies to fund clinical trials may be an overgeneralisation [6]. Venture capitalists have noted that short-term treatments for acute

diseases require shorter trials, and coupled with the higher approval ratings of antimicrobials, this may make antimicrobial development an attractive area for investment.

However, it does appear that for certain serious and life-threatening diseases, especially those caused by Gram-negative organisms more commonly found in the hospital setting, there are few drugs under development at the present time. Part of the issue with decreasing drug development is there are few new drugs to bring forward to develop. Many of the drugs under development by biotechnology firms are products that were discovered by larger pharmaceutical companies and licensed by biotechnology firms. As discussed above, it has been difficult to find new classes of antibacterial drugs. The promise of genomics in discovering new chemical entities has remained largely unfulfilled to date. It may be that this field will yield greater dividends in the future. In addition, some larger firms have dismantled the scientific infrastructure necessary for antimicrobial drug discovery. The question of addressing the need for further discovery efforts, whether by large pharmaceutical companies or smaller biotechnology firms, remains an important one.

Federal agencies are aware of the need to address the challenges related to antimicrobial resistance and to stimulate antimicrobial drug development. These agencies have been using their combined resources to attempt to address these issues. In 2001, a group of ten agencies chaired by the CDC, the FDA, and the National Institutes of Health (NIH) formed the Interagency Task Force on Antimicrobial Resistance. The Task Force put forward the Public Health Action Plan for Combating Antimicrobial Resistance [19], which includes specific agenda items addressing product development for diseases due to antimicrobial resistant pathogens.

The FDA has taken a number of steps in the last three years to address the issue of streamlining drug development for all drugs, and for antimicrobials in particular [1,18]. The Agency is putting forward revised guidelines for clinical trials of various infectious diseases, as requested by drug sponsors and by interested organisations. It is hoped that these guidelines will decrease uncertainty in the drug development process. These guidelines include recommendations for superiority trials in certain self-resolving diseases.

Trials that are designed to show the superiority of an antimicrobial to analgesics or decongestants in various upper respiratory tract illnesses can shrink the sample size necessary from the approximately 1500 patients in previous noninferiority trials reviewed by the FDA to approximately 400 patients for superiority trials. Given the largely self-resolving nature of many of these diseases, prescribing symptomatic therapies to all patients, and incorporating the administration of antimicrobials to patients who are failing to improve by specific time points ('early escape') should allow conduct of such trials with minimal risk to patients. The risk of a drug failing to demonstrate efficacy relative to placebo in such trials may be more substantial, but then again, this is exactly what the trial is supposed to be measuring. The regulatory standard for approval is demonstration that the study drug is more effective than placebo, and it would seem implausible that a drug would be more effective than an active control if it is not more effective than a placebo. In serious and life-threatening diseases, it is certainly appropriate and necessary to perform trials that show the similarity of new drugs to already approved agents. In such cases, the FDA has stated that there is no one universal noninferiority margin that is applicable to all diseases [14]. Rather, the FDA has afforded drug sponsors the opportunity to present scientific data on the margin of benefit of antimicrobials compared with placebo or no therapy in the disease under study in order to select an appropriate margin and justify the margin they have selected for their trials.

The FDA has also held several public workshops and advisory committee meetings addressing issues in reliance upon data from trials in one disease to lessen the number of trials necessary for approval in another disease [1,14,18]. The regulatory basis for approval is 'adequate and well-controlled trials'. This has been interpreted to mean more than one trial in a given disease, in order to confirm the results seen in a single trial. However, current regulations allow the approval of a drug for a given disease based on the results of a single study plus confirmatory evidence. At a recent advisory committee in March 2003, the FDA discussed a plan in which drug sponsors could perform two trials in a disease of sufficient severity, such as hospital-acquired or community-acquired pneumonia, to garner an approval [20].

Sponsors then could obtain subsequent approvals for other diseases with a single well-performed trial in other diseases. At the present time, regulations do not allow for approval of a drug for a disease without at least a single clinical study in that disease. There are exceptions for the rare circumstance where the disease is impossible to study or cannot be studied ethically. In such a case, as with inhalational anthrax, drugs may be approved according to data from animal studies alone. It seems inconsistent to claim that diseases due to resistant pathogens are an increasing problem and then state that they cannot be studied, so this 'animal rule' does not seem to apply to most bacterial diseases due to resistant pathogens.

On the other hand, to perform studies that include only patients with diseases caused by resistant pathogens can be challenging. As stated above, most disease is still caused by susceptible pathogens. Current diagnostic tests usually do not differentiate patients with disease due to resistant and susceptible bacterial pathogens prior to enrolment. Therefore, the FDA has approved drugs for diseases due to resistant pathogens by evaluating the efficacy of drugs for resistant pathogens within a given clinical trial for a particular disease [18]. For instance, the FDA has approved several drugs for community-acquired pneumonia (CAP) due to multi-drug-resistant *Streptococcus pneumoniae*. These approvals were based on an examination of [1]: the efficacy of the drug in the trials in CAP as a whole (due to all pathogens as well as those in whom a pathogen is not isolated) [2], evaluating the efficacy of the drug in CAP due to susceptible strains of *S. pneumoniae*, and [3] evaluating the efficacy of the drug in CAP caused by resistant strains. Given the differences in patient populations and host factors between those who have disease due to susceptible pathogens and those with resistant pathogens, it remains important to examine some amount of clinical information from patients with disease due to resistant pathogens. Similar *in vitro* activity does not always translate into similar *in vivo* efficacy. If the efficacy of the drug is similar in the various groups noted above, and there is supportive data from *in vitro* studies showing similar MICs of the drug for susceptible and resistant pathogens, as well as supportive data from animal studies, the drug can be approved for disease due to resistant

pathogens. Some drugs have been approved in this manner with as few as 14 isolates from patients with disease due to resistant pathogens. This obviates the need for drug sponsors to perform separate trials for disease due to resistant pathogens. However, it does require that sponsors make an effort to enrol patients from sites where resistant pathogens are more common so that they have a sufficient likelihood of enrolling patients with disease caused by these organisms. It is important to note that this analysis of efficacy in disease due to resistant pathogens is not comparing the efficacy of the new drug to the control drug, nor does it allow a claim of superiority of a new drug over the control based on a subgroup analysis. It is merely confirming similar efficacy of the study drug across various populations with disease caused by different pathogens. Drug sponsors may garner an approval for a drug for disease due to susceptible pathogens and then submit data related to disease due to resistant pathogens after approval. In this way, they may garner an approval for disease due to resistant pathogens at a later time without slowing the drug approval process.

The use of pharmacokinetic and pharmacodynamic (PK-PD) information is also important in the drug development process. In April 2004, the FDA cosponsored a workshop with the Infectious Diseases Society of America (IDSA) and the International Society of Anti-Infective Pharmacology (ISAP) where participants discussed these issues [18]. While PK-PD information is not a substitute for data from clinical trials, it can help in appropriate dose selection. Failure to select the appropriate dose can result in the failure to demonstrate efficacy of a new drug and create the need to perform further clinical trials, with the resulting increased expense. At the meeting, participants discussed the tendency for drug sponsors to skip the Phase II trials that are often necessary in selecting the appropriate dose, in order to speed the drug development process. It is not clear whether this need for speed in the long run is resulting in longer development times for new drugs if sponsors proceed to larger, more expensive Phase III clinical trials without knowing the proper dose of antimicrobial to use in the trial. Phase II trials may be a wise investment in the long run if they prevent the failure of larger, more expensive Phase III trials.

Also during the April workshop, participants discussed the use of surrogate endpoints for demonstrating the efficacy of antimicrobials in clinical trials [18]. These surrogate endpoints are often microbiological measurements of the presence or absence of the causative pathogen at some time after the initiation of therapy. The current regulations allow the FDA to approve a drug based on surrogate endpoints that have already been validated to demonstrate clinical benefit to patients. Clinical benefit means improvements in how the patient feels, functions or survives. If the surrogate endpoint has not been validated, the FDA can grant an 'accelerated approval' if the disease under study is a serious and life-threatening disease and the surrogate is reasonably likely to predict a clinical benefit. Drug sponsors then must still complete trials that show that the surrogate indeed translates into a clinical benefit for patients. It has become clear that surrogates are most useful in chronic diseases. For short-term illnesses, it is often just as easy, if not easier, to measure clinical outcomes as it is to measure the surrogate endpoint. In short-term diseases, confirming the surrogate would require initiation of further trials, rather than continuing to follow patients as done with chronic diseases.

In March 2004, the FDA put forward an initiative called the 'Critical Path' to drug development [5]. The focus of this initiative is on developing better tools to measure the safety and efficacy of drugs. These tools may be helpful in selecting drugs that are more likely to succeed in demonstrating safety and efficacy in clinical trials. In addition, better tools can eliminate drugs that are likely to fail early in the development process, thus decreasing the costs of these failed drugs that contribute so much at the present time to the overall costs of drug development. Tools such as better diagnostic testing could increase the efficiency of clinical trials for infectious diseases. For many infectious diseases, it is quite difficult to differentiate bacterial vs. viral disease. The inclusion of large numbers of patients with viral disease may dilute the treatment effects of antibacterial drugs. Also, drug sponsors may require a greater number of patients to enrol sufficient numbers who truly have bacterial disease. In an FDA review of clinical trials of acute bacterial sinusitis, as few as 36% of enrolled patients

actually had bacterial disease when defined by sinus puncture [21]. In addition, new tools for measuring clinical outcomes in patients, such as patient reported outcome scales (PROs), may be useful in more accurate measurements of clinical endpoints. FDA guidance on developing such tools is forthcoming.

CONCLUSIONS

There is clearly a need for new antimicrobials to combat disease due to resistant pathogens in serious and life-threatening diseases. Federal agencies are attempting to do their part in addressing this need. However, streamlining the regulatory process will not be useful unless there are new drugs to put forward on the development pathway. This will take an increased effort in the area of drug discovery, which is beyond the scope of a regulatory agency. While the FDA is attempting to streamline the drug development process, these changes cannot turn a \$2 bn drug into a \$9 bn drug. To stimulate drug development appears to require economic incentives for drug sponsors that can only be accomplished by changes in legislation. Such incentives should attempt to channel resources towards discovery and development for those diseases where there is the greatest need, such as serious infections in hospitalised patients. The FDA has put forward several suggestions for streamlining clinical trial design, allowing smaller sample sizes for individual clinical trials, as well as for overall drug development programmes, while maintaining the standards that clinicians and patients expect and deserve. 'Creative' clinical trial design does not imply lower standards and any changes put forward by the FDA must be within the bounds of current regulations. The economic needs of the pharmaceutical industry still must be balanced against the imperative to protect and advance public health. Improved clinical trial design requires the use of better tools in the drug development process to evaluate efficacy and safety. It is not the role of the FDA to develop the tools necessary to move drugs forward, but the Agency's breadth of experience in evaluating both successful and unsuccessful drug development programmes can help to guide researchers in the development of such tools. While there remain significant challenges in the discovery and development of new antimicrobials, there are still

advantages for those willing to continue to advance the science and public health in this field.

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